

# The disposition of fluoxetine but not sertraline is altered in poor metabolizers of debrisoquin

**Background:** Substrates and inhibitors of the cytochrome P450 isozyme CYP2D6 have overlapping structural characteristics. Two prototype serotonin uptake inhibitors, sertraline and fluoxetine, share these structural criteria and have been identified as potent inhibitors of CYP2D6 in vitro. The current study was undertaken to investigate whether genetically determined CYP2D6 activity alters the disposition of sertraline or fluoxetine or both.

**Methods:** Single doses of sertraline (50 mg) and fluoxetine (20 mg) were administered successively to 20 young men with high (extensive metabolizers;  $n = 10$ ) and low (poor metabolizers;  $n = 10$ ) CYP2D6 activity. Blood and urine samples were collected for 5 to 7 half-lives and sertraline, desmethylsertraline, fluoxetine, and norfluoxetine were determined by GC and HPLC techniques.

**Results:** Poor metabolizers had significantly greater fluoxetine peak plasma concentrations ( $C_{max}$ ;  $\uparrow 57\%$ ), area under the concentration versus time curve ( $AUC_{0-\infty}$ ;  $\uparrow 290\%$ ), and terminal elimination half-life ( $\uparrow 216\%$ ) compared with extensive metabolizers. The total amount of fluoxetine excreted in the urine during 8 days was almost three times higher in poor metabolizers than in extensive metabolizers (719 versus 225  $\mu\text{g}$ ;  $p < 0.05$ ), whereas the total amount of norfluoxetine excreted in urine of poor metabolizers was about half of that of extensive metabolizers (524 versus 1047  $\mu\text{g}$ ;  $p < 0.05$ ). Norfluoxetine  $C_{max}$  and  $AUC_{0-\infty}$  were significantly smaller in poor metabolizers ( $\downarrow 55\%$  and  $\downarrow 53\%$ , respectively), and the partial metabolic clearance of fluoxetine into norfluoxetine was 10 times smaller in this group ( $4.3 \pm 1.9$  versus  $0.4 \pm 0.1$  L/hr;  $p < 0.05$ ). No significant differences between extensive and poor metabolizers were found for sertraline and desmethylsertraline pharmacokinetics.

**Conclusion:** These data indicate that poor metabolizers accumulate fluoxetine but not sertraline and that CYP2D6 plays an important role in the demethylation of fluoxetine but not of sertraline. (Clin Pharmacol Ther 1996;60:512-21.)

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Fluoxetine and sertraline are potent and selective serotonin reuptake inhibitors with antidepressant properties.<sup>1,2</sup> Although these compounds have the same mechanism of action, fluoxetine differs structur-

ally from sertraline in that fluoxetine is a derivative of phenylpropanolamine and sertraline is a derivative of tetrahydronaphthylamine (see Structure).<sup>3,4</sup>

Fluoxetine and sertraline are extensively metabolized by liver metabolic enzymes, and less than 2.5% of both drugs are recovered unchanged in the urine.<sup>3,5-7</sup> The major metabolites currently known in humans are *N*-dealkylation products; namely, the active norfluoxetine<sup>3,5</sup> and the inactive desmethylsertraline.<sup>7</sup> Fluoxetine and norfluoxetine can be further glucuronidated, whereas major metabolites of sertraline may also include *N*-hydroxysertraline and a ketone that is further hydroxylated.<sup>6,7</sup> However, the majority of fluoxetine and sertraline metabolites in humans are currently unknown,<sup>1,7</sup> and the

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Supported by Pfizer Inc. (Groton, Conn.) and by the Medical Research Council of Canada (Ottawa, Ontario; MA-11876, MT-13263).

Received for publication Dec. 6, 1995; accepted June 27, 1996.

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0009-9236/96/\$5.00 + 0 13/1/76073

isozymes responsible for the production of their known metabolites have not been identified.

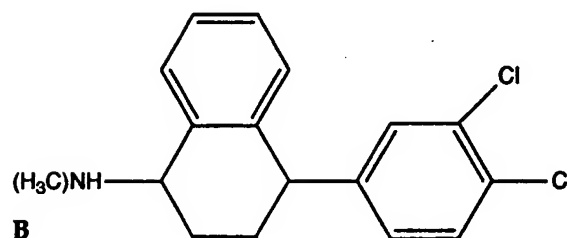
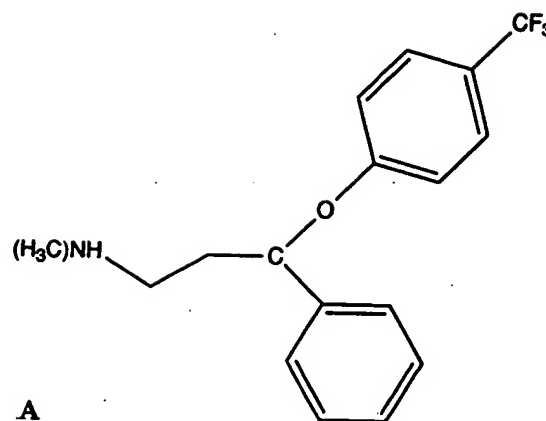
CYP2D6 is a cytochrome P450 isozyme responsible for the metabolism of a variety of agents, including a number of antidepressant and antipsychotic drugs.<sup>8,9</sup> CYP2D6 activity is genetically determined, and the general white population can be separated into 5% to 10% poor metabolizers and 90% to 95% extensive metabolizers.<sup>8</sup> Poor metabolizers are at increased risk for the accumulation of drugs, resulting in drug-related toxicity or lack of therapeutic efficacy.<sup>8</sup> In vitro studies with use of human liver microsomes have shown that fluoxetine and sertraline are potent inhibitors of CYP2D6.<sup>10-12</sup> Clinically, this inhibition has been observed with fluoxetine<sup>13-16</sup> but not with sertraline,<sup>17,18</sup> most likely because plasma concentrations achieved after clinically effective doses are much higher after fluoxetine than after sertraline administration.<sup>19</sup>

Whether CYP2D6 plays a role in the metabolism of fluoxetine and sertraline is still unknown. In vivo pharmacokinetic data for fluoxetine have shown large interindividual variability consistent with CYP2D6 polymorphic characteristics.<sup>3,5,20-22</sup> Some, but considerably less, intersubject variability was associated with sertraline administration.<sup>2,17,18</sup> It was therefore our objective to determine whether CYP2D6 activity alters the pharmacokinetics of fluoxetine or sertraline or both.

## METHODS

This was an open-label two-period study to assess the disposition of fluoxetine and sertraline in 20 known extensive and poor metabolizers of debrisoquin (debrisoquine). All participants were healthy male nonsmokers. Each volunteer received both study drugs on two separate occasions. The study was approved by the Laval University Ethics Committee. All volunteers gave informed consent before participation in the study.

The CYP2D6 phenotype of healthy volunteers eligible for the study was determined by a standard procedure.<sup>23,24</sup> In brief, each volunteer self-administered a single oral 10 mg dose of debrisoquin at bedtime and was asked to collect urine over an 8-hour period. Debrisoquin and 4-hydroxydebrisoquin urine concentrations were determined by gas chromatography with flame ionization detection with use of a DB-5 microbore column (Chromatography Specialties Inc., Brookville, Ontario). Guanoan was used as internal standard.<sup>24</sup> A urinary metabolic ratio of 4-hydroxydebrisoquin/de-



Structures of fluoxetine (top) and sertraline (bottom).

brisoquin greater than 12.6 is consistent with the poor metabolizer phenotype.

Ten extensive metabolizers and 10 poor metabolizers were selected from a phenotyped volunteers pool for participation in the study. All individuals were healthy as determined by medical history, physical examination, and laboratory screening performed within 2 weeks before study entry. Exclusion criteria included history of significant illness that could have affected the outcome of the investigation, for example, liver or heart disease, abuse of drugs and alcohol, positive smoking history (i.e., evidence of smoking within the previous 2 years), prescription or over-the-counter drugs within 7 days before the study, participation in investigational drug studies within 4 weeks before the study, blood donations within 3 months before the study, history of noncompliance, and history of seizures.

Participants reported to the research facility in the morning of each study period after an overnight fast. Subjects were confined to the research facility during the first 16 hours of each study period and

**Table I.** Demographic and phenotyping data of 20 healthy poor and extensive metabolizers of debrisoquin (debrisoquine)

Subject No.	Age (yr)	Weight (kg)	Height (cm)	Debrisoquin/4-hydroxydebrisoquin
<i>Extensive metabolizers</i>				
01	22	68	165	0.92
02	19	63	173	0.37
03	28	74	176	2.17
04	26	66	175	1.5
05	19	65	183	0.73
06	28	67	169	0.30
07	18	59	166	4.08
08	21	67	171	0.40
09	24	65	181	0.17
10	19	69	177	0.18
Mean $\pm$ SD	22 $\pm$ 4	66 $\pm$ 4	173 $\pm$ 6	1.08 $\pm$ 1.2
<i>Poor metabolizers</i>				
11	32	62	168	>100
12	22	84	185	49.3
13	18	77	173	>100
14	33	76	190	>100
15	31	46	168	>100
16	22	61	173	20
17	33	73	179	>100
18	24	84	179	>100
19	22	73	173	>100
20	18	59	172	>100
Mean $\pm$ SD	26 $\pm$ 6	69 $\pm$ 12	176 $\pm$ 7	—

were not allowed to lie down for the first 4 hours after drug administration. During confinement, only nonstrenuous activity was permitted. Study period 1 consisted of administration of a single 50 mg dose of sertraline with 240 ml water to all volunteers. Blood was collected at 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 48, 72, 96, 120, and 144 hours after drug administration. Urine was collected in six 24-hour urine collections. During the second study period, all participants received a single 20 mg dose of fluoxetine with 240 ml water. Blood was collected at 0, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 16, 24, 36, 48, 72, 96, 120, 144, 168, and 192 hours after administration of the drug. Urine was collected in eight 24-hour urine collections. The sequential administration of sertraline followed by fluoxetine, the length of collection times during the two study periods, and the 2-week washout between the study periods were chosen to respect individual drug half-lives.

Sertraline and desmethylsertraline plasma concentrations were determined by a modified electron-capture gas liquid chromatographic assay.<sup>25</sup> In brief, the internal standard (CP-53,680) was added to all samples that contained sertraline and desmethylser-

traline. Samples were adjusted to pH > 10.5, then extracted with diethylether/hexane (80:20), and re-extracted into the aqueous phase with sulfuric acid. Subsequently derivatives were formed with trifluoroacetic acid in diethylether hexane, and residues were reconstituted with methanol and then injected into a gas liquid chromatograph equipped with electron-capture detector. The detection limits were 1  $\mu$ g/L (interassay coefficient of variation [CV], 2.6%) for sertraline and 2  $\mu$ g/L (interassay CV, 4.2%) for desmethylsertraline. Calibration curves ranged from 1 to 50  $\mu$ g/L for sertraline and 2 to 40  $\mu$ g/L for desmethylsertraline. Intraassay accuracy as determined by the percent relative error ranged from -2.7% to 0.6% for sertraline and from -6.9% to 8.1% for desmethylsertraline; intraassay precision as determined by coefficient of variation ranged from 2.9% to 4.4% for sertraline and 2.0% to 5.3% for desmethylsertraline; interassay accuracy ranged from -1.4% to 1.4% for sertraline and from -1.8% to 1.2% for desmethylsertraline; interassay precision ranged from 4.6% to 5.7% for sertraline and 5.7% to 7.3% for desmethylsertraline. Concentrations in the urine were too low to be detected by this method.

**Table II.** Pharmacokinetic parameters of fluoxetine, norfluoxetine, sertraline, and desmethylsertraline after single doses of the parent compounds to poor metabolizers and extensive metabolizers of debrisoquin

Parameter	Fluoxetine		Norfluoxetine		Sertraline		Desmethylsertraline	
	EM*	PM†	EM*	PM†	EM†	PM†	EM†	PM†
$C_{max}$ ( $\mu\text{g/L}$ )	14 $\pm$ 3	22 $\pm$ 5‡	11 $\pm$ 3	5 $\pm$ 1‡	16 $\pm$ 2	17 $\pm$ 5	9 $\pm$ 2	8 $\pm$ 3
$t_{max}$ (hr)	6 $\pm$ 2	7 $\pm$ 1	44 $\pm$ 32	79 $\pm$ 39‡	6 $\pm$ 2	7 $\pm$ 1	9 $\pm$ 2	11 $\pm$ 3
$AUC_{0-\infty}$ ( $\mu\text{g} \cdot \text{hr/L}$ )	481 $\pm$ 245	1871 $\pm$ 328‡	1579 $\pm$ 396	736 $\pm$ 148‡	441 $\pm$ 231	447 $\pm$ 161	742 $\pm$ 395	535 $\pm$ 236
$\lambda_z$ ( $\text{hr}^{-1}$ )	0.03 $\pm$ 0.01	0.009 $\pm$ 0.002‡	—	—	0.038 $\pm$ 0.019	0.032 $\pm$ 0.008	—	—
$t_{1/2\lambda_z}$ (hr)	24 $\pm$ 7	76 $\pm$ 14‡	—	—	27 $\pm$ 20	24 $\pm$ 6	—	—
Ae ( $\mu\text{g}$ )	225 $\pm$ 89	719 $\pm$ 208‡	1047 $\pm$ 292	524 $\pm$ 173‡	—	—	—	—
$CL_R$ (L/hr)	0.7 $\pm$ 0.4	0.5 $\pm$ 0.2	0.7 $\pm$ 0.4	0.5 $\pm$ 0.2	—	—	—	—
$CL_{FXT \rightarrow NFX}$ (L/hr)	—	—	4.3 $\pm$ 1.9	0.4 $\pm$ 0.1‡	—	—	—	—

Data are mean values  $\pm$  SD. $C_{max}$ , Peak plasma concentration;  $t_{max}$ , time to reach  $C_{max}$ ; AUC, area under the plasma concentration-time curve;  $\lambda_z$ , elimination rate constant;  $t_{1/2\lambda_z}$ , terminal elimination half-life; Ae, amount of drug excreted unchanged in urine;  $CL_R$ , renal clearance;  $CL_{FXT \rightarrow NFX}$ , partial metabolic clearance of fluoxetine to norfluoxetine.

\*n = 9 subjects.

†n = 10 subjects.

‡p &lt; 0.05 versus extensive metabolizers.

Fluoxetine and norfluoxetine concentrations in plasma and urine were determined by a modified reversed-phase HPLC method.<sup>26</sup> In brief, after addition of the internal standard (clomipramine) samples were extracted with heptane/isoamyl alcohol (98:2), back-extracted with 200  $\mu\text{L}$  hydrochloric acid (100 mmol/L) and then injected into an HPLC equipped with an ultraviolet detector ( $\lambda = 226 \text{ nm}$ ). Quantitation limits were 2  $\mu\text{g/L}$  for both fluoxetine and norfluoxetine, with interassay coefficients of variation ranging from 2% to 4%. Intraassay accuracy as determined by the percent relative error ranged from -8.2% to 8.9%, and intraassay precision as determined by coefficient of variation ranged from 4.4% to 9.5% for both fluoxetine and norfluoxetine. Interassay accuracy ranged from -2.4% to 6.3% and interassay precision from 4.5% to 6.6% for both fluoxetine and norfluoxetine.

**Data analysis.** A noncompartmental approach<sup>27</sup> was chosen to determine fluoxetine and sertraline elimination rate constants by using the best fit from 8 hours after drug administration on until the end of the study. Area under the concentration versus time curve ( $AUC_{0-\infty}$ ) was calculated for drugs and metabolites with use of the linear trapezoidal rule for ascending data and the log-trapezoidal rule for descending data with the terminal portion extrapolated to infinity. Renal clearance values of fluoxetine were calculated as the ratio of the amount of drug excreted unchanged in urine (Ae) over 192 hours and the AUC of the drug over the same time interval. Partial metabolic clearance of fluoxetine to nor-

fluoxetine ( $CL_{FXT \rightarrow NFX}$ ) was calculated on a molar basis by dividing the total amount of the metabolite found in urine by the  $AUC_{0-192}$  of fluoxetine. The Student *t* test and Mann-Whitney *U* test were used to compare the two groups, depending on data variance.

## RESULTS

Ten extensive metabolizers (mean age, 22.4  $\pm$  3.9 years) and 10 poor metabolizers (mean age, 25.5  $\pm$  6.1 years) from our phenotyped pool of healthy volunteers were included in the study. Nineteen subjects completed both study periods. One extensive metabolizer did not participate in the fluoxetine portion of the investigation. None of the subjects experienced adverse effects related to either study medication. Demographic and phenotyping data are summarized in Table I. There was no difference with respect to age, weight, or height between extensive and poor metabolizers of debrisoquin.

Pharmacokinetic parameters of sertraline and desmethylsertraline did not differ between extensive and poor metabolizers of debrisoquin (Table II; *p* > 0.05). Sertraline and desmethylsertraline plasma concentrations obtained in an extensive metabolizer and a poor metabolizer are shown in Fig. 1. Maximum sertraline plasma concentrations of approximately 16  $\mu\text{g/L}$  were achieved at 6 to 7 hours after administration of the 50 mg oral dose of the drug. The elimination half-life ( $t_{1/2\lambda_z}$ ) of sertraline was 27 and 24 hours in extensive metabolizers and poor metabolizers, respectively. Desmethylsertraline reached maximum serum concentrations of about

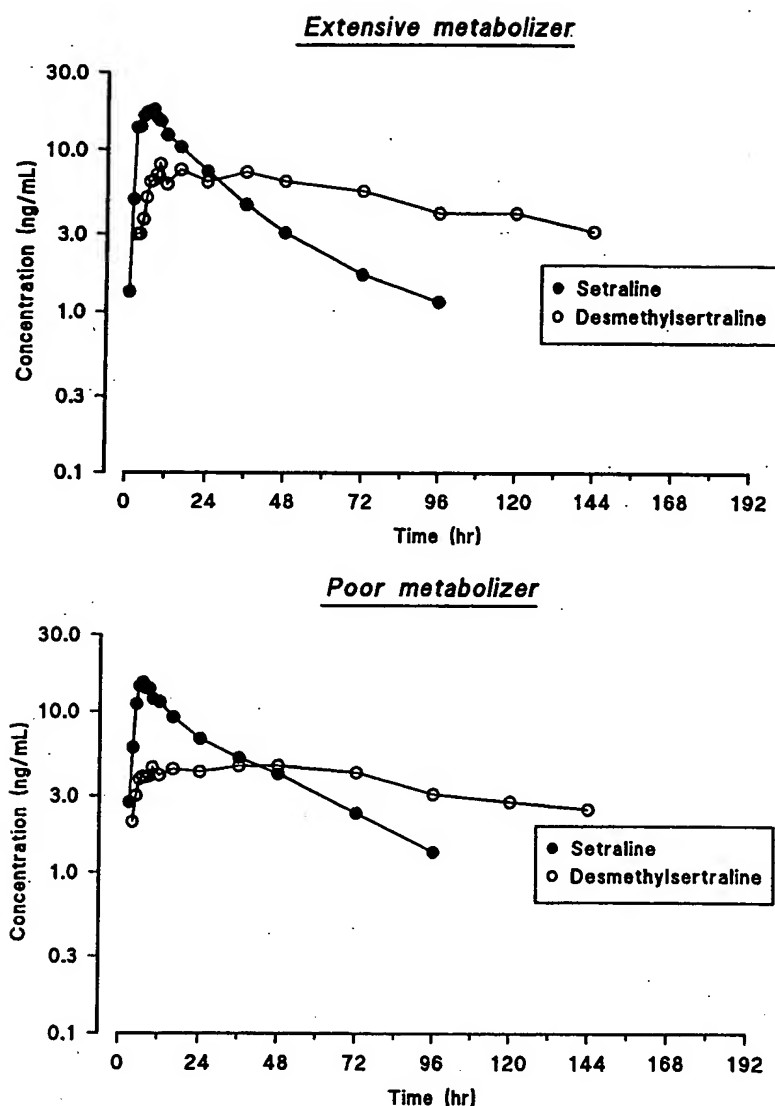


Fig. 1. Plasma concentration-time profile of sertraline and desmethylertraline in an extensive and a poor metabolizer of debrisoquin (debrisoquine).

8  $\mu\text{g/L}$  between 8 and 10 hours after administration of sertraline in both study groups.

In contrast, marked differences in the pharmacokinetic disposition of fluoxetine and norfluoxetine between poor metabolizers and extensive metabolizers were found (Table II; Fig. 2). Poor metabolizers had a 57% increase in  $C_{\text{max}}$  ( $p < 0.05$ ), a 290% increase in  $\text{AUC}_{0 \rightarrow \infty}$  ( $p < 0.05$ ), and a 216% increase in terminal elimination half-life ( $t_{1/2\lambda z}$ ) ( $p < 0.05$ ) compared with extensive metabolizers. The total amount of fluoxetine excreted in the urine during the 8-day collection

interval was almost three times higher in poor metabolizers compared with extensive metabolizers ( $719 \pm 208$  versus  $225 \pm 89$   $\mu\text{g}$ ;  $p < 0.05$ ). During the same time interval the total amount of norfluoxetine excreted in urine of poor metabolizers was about half of that of extensive metabolizers ( $524 \pm 173$   $\mu\text{g}$  in poor metabolizers versus  $1047 \pm 292$   $\mu\text{g}$  in extensive metabolizers;  $p < 0.05$ ). In addition, norfluoxetine  $C_{\text{max}}$  and  $\text{AUC}_{0 \rightarrow 192}$  were significantly smaller in poor metabolizers ( $\downarrow 55\%$  and  $\downarrow 53\%$ , respectively) compared with extensive metabolizers. Consequently,

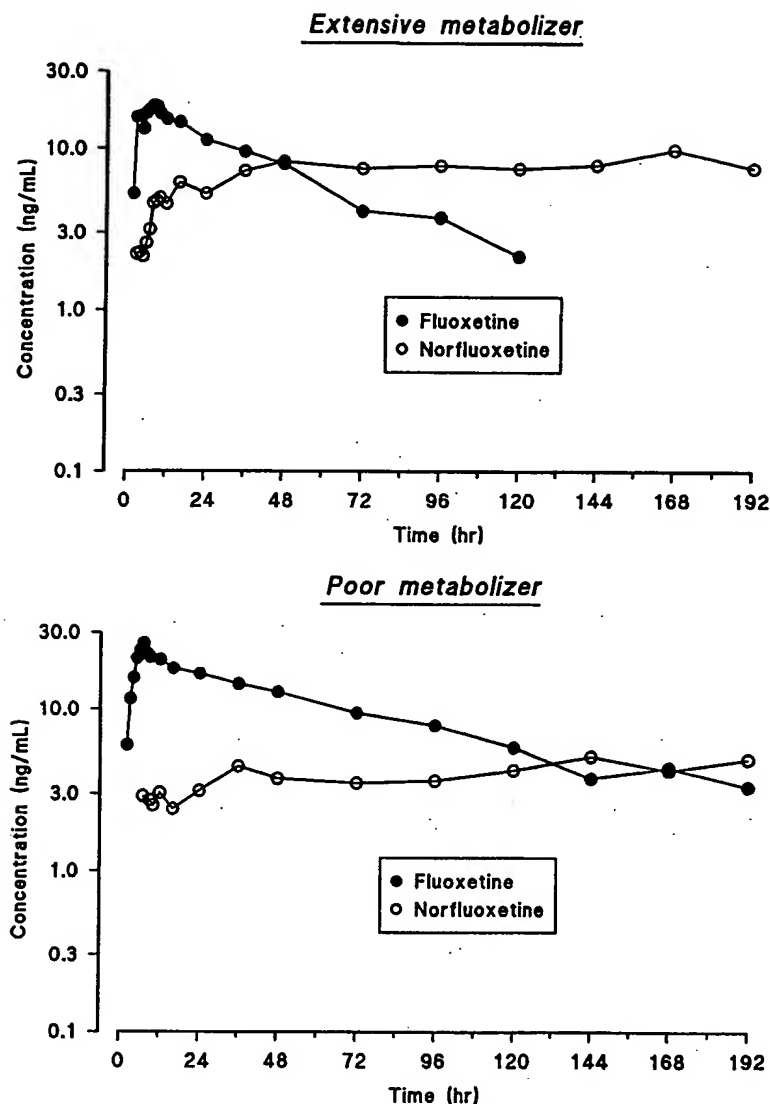


Fig. 2. Plasma concentration-time profile of fluoxetine and norfluoxetine in an extensive and a poor metabolizer of debrisoquin.

partial metabolic clearance of fluoxetine into norfluoxetine was 10 times smaller in poor metabolizers ( $0.4 \pm 0.1$  versus  $4.3 \pm 1.9$  L/hr;  $p < 0.05$ ). The renal clearance of fluoxetine and norfluoxetine did not differ between groups.

The involvement of CYP2D6 in the pharmacokinetics of fluoxetine was also assessed by correlating the debrisoquin/4-hydroxydebrisoquin metabolic ratio as a marker of CYP2D6 activity with the fluoxetine/norfluoxetine metabolic ratios. These metabolic ratios correlated significantly (Fig. 3), not only between extensive metabolizers and poor metabo-

lizers ( $r = 0.925$ ;  $p < 0.0001$ ) but also within the extensive metabolizer phenotype group ( $r = 0.731$ ;  $p < 0.05$ ).

## DISCUSSION

To our knowledge, this is the first investigation that describes the role of the genetically determined CYP2D6 activity in the disposition of fluoxetine and sertraline in humans. We found that CYP2D6 has a significant impact on the disposition of fluoxetine but not of sertraline and that CYP2D6 appears to be capable of catalyzing *N*-demethylation reactions of

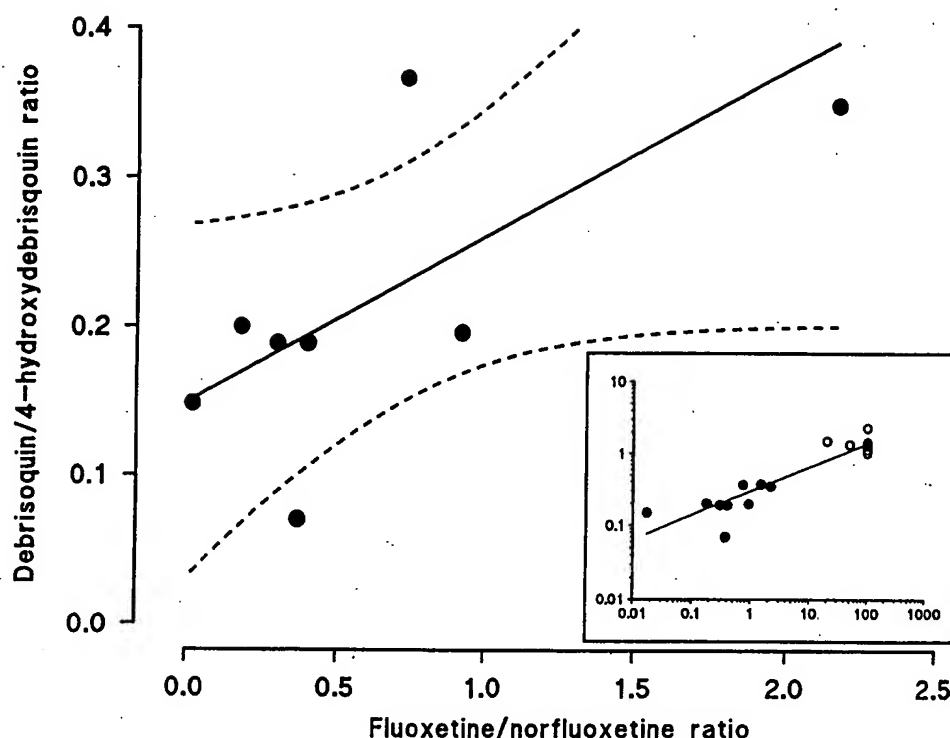


Fig. 3. Correlation between the debrisoquin/4-hydroxydebrisoquin metabolic ratios and the fluoxetine/norfluoxetine metabolic ratios among the extensive metabolizer group ( $r = 0.731$ ;  $p < 0.05$ ) and among extensive and poor metabolizers (inset:  $r = 0.925$ ;  $p < 0.0001$ ).

certain CYP2D6 substrates (fluoxetine) but not of others (sertraline).

Although early interaction studies in humans showed no clinically significant effect of fluoxetine on the pharmacokinetics of warfarin, diazepam, chlorothiazide, and tolbutamide,<sup>1</sup> it is now well established that fluoxetine is a potent inhibitor of a specific cytochrome P450 isozyme, namely CYP2D6, in vitro and in vivo.<sup>10,11,19</sup> Numerous reports indicate that fluoxetine interacts with known CYP2D6 substrates and inhibitors, such as tricyclic antidepressants,<sup>13,28-30</sup> dextromethorphan,<sup>31</sup> and antipsychotics.<sup>32,33</sup> Recently it was shown that fluoxetine may also inhibit CYP3A4<sup>34</sup> and CYP2C<sup>19</sup> isozymes and interactions of fluoxetine with terfenadine (CYP3A4 substrate)<sup>35</sup> and with phenytoin (partially metabolized by the CYP2C family)<sup>36</sup> have been reported. On the other hand, preclinical and clinical single-dose studies aimed at the evaluation of potential interactions between sertraline and drugs such as antipyrine, warfarin, tolbutamide, atenolol,

alcohol, diazepam, or digoxin showed no significant effects of sertraline on the disposition and therapeutic efficacy of these compounds.<sup>2</sup> In vitro, sertraline was a potent inhibitor of CYP2D6.<sup>10</sup> However, this effect appeared to be much less important in vivo. This was probably due to its low concentrations at enzymatic receptor sites after clinically used doses.<sup>19</sup> Thus, in contrast to fluoxetine, sertraline appears to have a less-intense and briefer effect on tricyclic antidepressant plasma levels.<sup>19</sup>

A review of known CYP2D6 substrates has revealed common structural features: (1) a region of negative electrostatic potential in proximity of the oxidation site, (2) a basic nitrogen at a distance of 5 to 7 Å from the oxidation site, and (3) an alignment of the substrate so that there is a planar region near the oxidation site. It was proposed that binding to CYP2D6 is governed by an ion-pair formation between the basic nitrogen of the substrate or inhibitor and one or the other of the carboxylic oxygens of the carboxylate group on the protein. Oxidation would

then be expected at 5 to 7 Å from the basic nitrogen.<sup>37,38</sup> This suggests that fluoxetine and sertraline aromatic oxidation but not *N*-dealkylation would be predictive pathways of CYP2D6.

On the other hand, it was suggested that CYP2D6 may be involved in *N*-demethylation reactions.<sup>11,39</sup> It was shown previously that, in vitro, (*R*)- and (*S*)-fluoxetine *N*-demethylase activities in human liver microsomes correlated significantly with levels of immunodetectable CYP2D6 ( $r = 0.64$ ;  $p < 0.05$ ).<sup>11</sup> However, because selective CYP2D6 inhibition with either quinidine or CYP2D6 antiserum resulted in 60% to 80% uninhibited demethylation activity in vitro, these investigators proposed that isozymes other than CYP2D6, namely CYP3A4, may be primarily responsible for the fluoxetine demethylation reaction in vivo.<sup>11</sup> *N*-Dealkylation of several other substrates appears to be mediated by CYP2D6. For example, CYP2D6 contributed to imipramine demethylation (in vitro and in vivo), didesmethylcitalopram formation (in extensive metabolizers but not in poor metabolizers), and in vitro formation of nortriptyline and 10-hydroxynoramitriptyline.<sup>39</sup> As a consequence, it was suggested that a 3-carbon unbranched aliphatic chain between the ring system and the nitrogen atom where *N*-demethylation occurs may be a necessary feature for CYP2D6 related *N*-demethylation.<sup>39</sup>

Pharmacokinetic parameters derived in this current investigation are in agreement with previously published data for sertraline<sup>2,22</sup> and for fluoxetine.<sup>3,5,20,21,40</sup> In addition, our data suggest that CYP2D6 is an important mediator of the *N*-demethylation of fluoxetine at the amino group leading to norfluoxetine. The fluoxetine/norfluoxetine metabolic ratios correlated significantly with the debrisoquin/4-hydroxydebrisoquin metabolic ratios among extensive and poor metabolizers (Fig. 3). These results may support the hypothesis of Coutts et al.,<sup>39</sup> for it can be observed that fluoxetine has a 3-carbon aliphatic chain, whereas sertraline does not.

On the other hand, although enzyme substrates will usually also inhibit the same enzyme, enzyme inhibitors are not necessarily also substrates of the same enzyme. An example is quinidine, a potent and selective inhibitor of CYP2D6 that is not metabolized by this enzyme.<sup>41-44</sup> The similar concentration-time profiles of sertraline among poor metabolizers and extensive metabolizers lead us to suggest that despite its low inhibitory

constant ( $K_i$ ) for CYP2D6, this enzyme does not play a role in sertraline disposition, in a similar way CYP2D6 can not metabolize its potent inhibitor quinidine.

In conclusion, we investigated the disposition of fluoxetine and sertraline and their major metabolites in 20 healthy volunteers with either high or low activity of the genetically determined CYP2D6 activity. We observed no effect of CYP2D6 activity in vivo on sertraline or desmethylsertraline pharmacokinetics. In contrast, there were significant differences in the disposition of fluoxetine and norfluoxetine between poor and extensive metabolizers, with poor metabolizers accumulating fluoxetine while formation of the *N*-demethylated major active metabolite of fluoxetine, norfluoxetine, was reduced. These data suggest that CYP2D6 plays an important role in the disposition of fluoxetine but not of sertraline and that CYP2D6 contributes significantly to the *N*-demethylation of fluoxetine. Thus, poor metabolizers appear to be at increased risk for accumulation of fluoxetine and the possible development of fluoxetine-associated toxicity. In addition, poor metabolizers may lack norfluoxetine's beneficial contributions to the overall clinical effect of fluoxetine therapy.

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